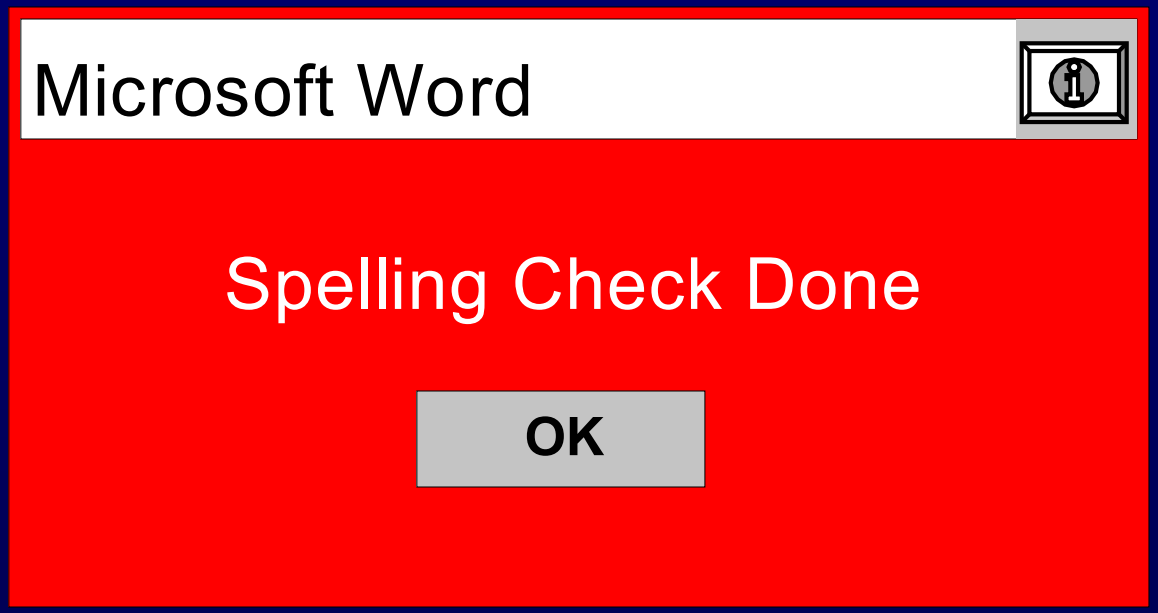
Every thin hear is spilled write



General toxicology objectives

The student should be able to

- Describe how chemicals harm creatures
- Explain the difference between a poison and a hazard
- Explain the factors that influence toxicity

How chemicals harm

- a)Flammable/Explosive e.g., gasoline, nitroglycerin
- b)Corrosive e.g., strong acids and bases
- c)Irritants e.g., mild acids and bases
- d)Sensitization e.g., allergies such as Rhus dermatitis
- e)Internal damage e.g., Benzene

Definitions

- Hazard - a complex term relating both
  - inherent ability to do harm
  - plus consideration for the likelihood or contact, ingestion or dosage

Factors that influence toxicity

Properties of the substance

- Toxic qualities
- Quantities
  - Stay in - lipid solubility and small size
  - Get rid of - water solubility and small size
- Route of exposure- Skin / Lungs / GI tract

Factor that influence toxicity

Properties of the target

- Species
- Age
- Sex
- Individual
- Chemical Interactions - Synergistic (and antagonistic) chemicals
- Adaptation

Objectives for immunotoxicology

The student should be able to understand/explain/recognize

- Innate v. acquired immunity
- Cellular v. humoral immunity
- Differences between type I and type IV hypersensitivity
- Recognize common occupational diseases due to hypersensitivity
- Basic thoughts behind multiple chemical sensitivities

Innate v. Acquired

- Innate immunity nonspecific
  - it includes physical and biochemical barriers
- Acquired immunity
  - Activated when innate immunity fails
  - Specificity and memory

Type I Reaction with IGE

antibodies bound to mast cells and basophils

- Mast cells release histamine and other compounds
- Bronchoconstriction, vasodilation, capillary permeability
- Lots of inflammation

Type I

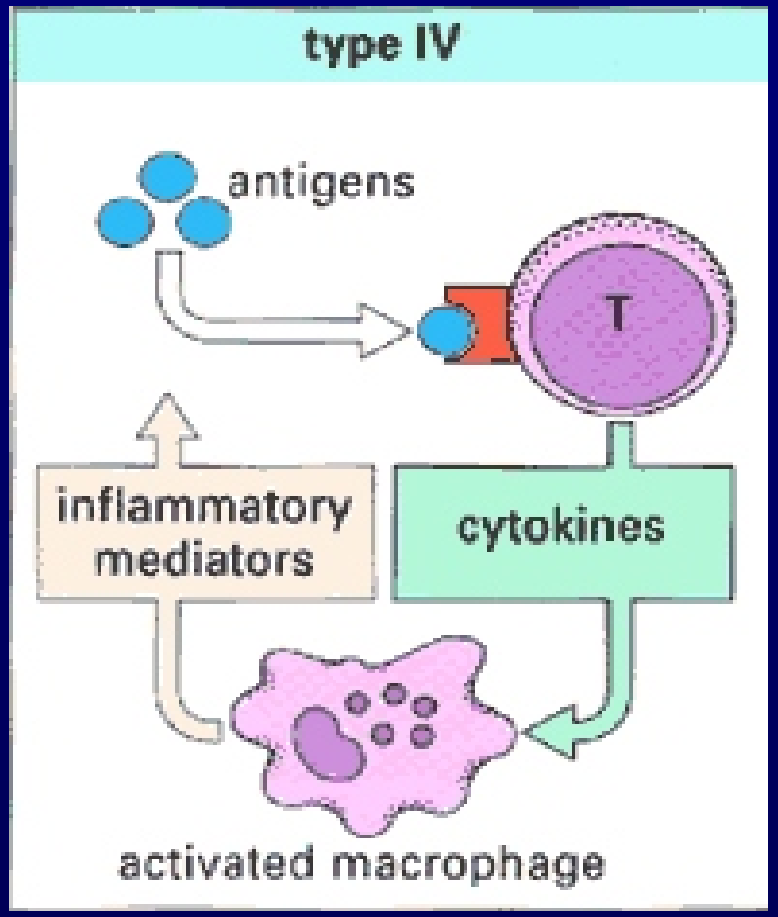
- Atopic people react to large MW
- Anyone can be sensitized to low MW products like TDI (Toluene di-isocyanate) and Platinum salts, cobalt
- Asthma symptoms may be delayed

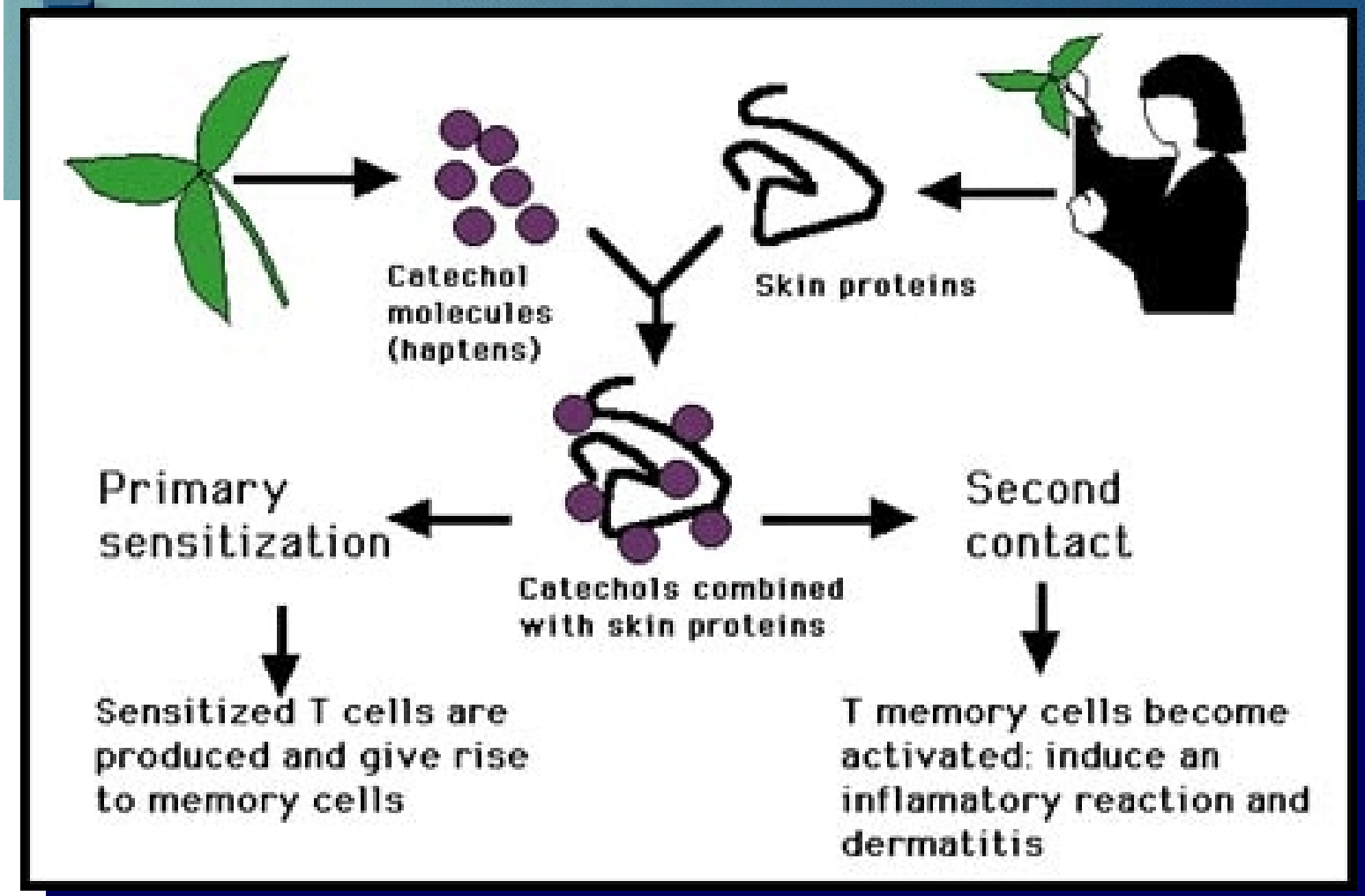
Items likely to cause Type I in a DoD setting

- Latex allergy
  - Food allergy (banana, avocado, passion fruit, chestnut, kiwi fruit, melon, tomato, celery)
- Wood dusts, especially in Civil Engineering staff
- Animal danders, especially in PHO veterinarians
- Lawn Molds - ground crew workers
- Isocyanates - paints and varnishes
- Epoxy resins - composites.
- Formaldehyde - hospital workers, esp in path labs

Type IV Cellular immunity

contact dermatitis, TB tests




Catechol molecules (haptens)
Skin proteins
Primary sensitization
Catechols combined with skin proteins
Second contact
Sensitized T cells are produced and give rise to memory cells
T memory cells become activated: induce an inflamatory reaction and dermatitis

Objectives for skin toxicology

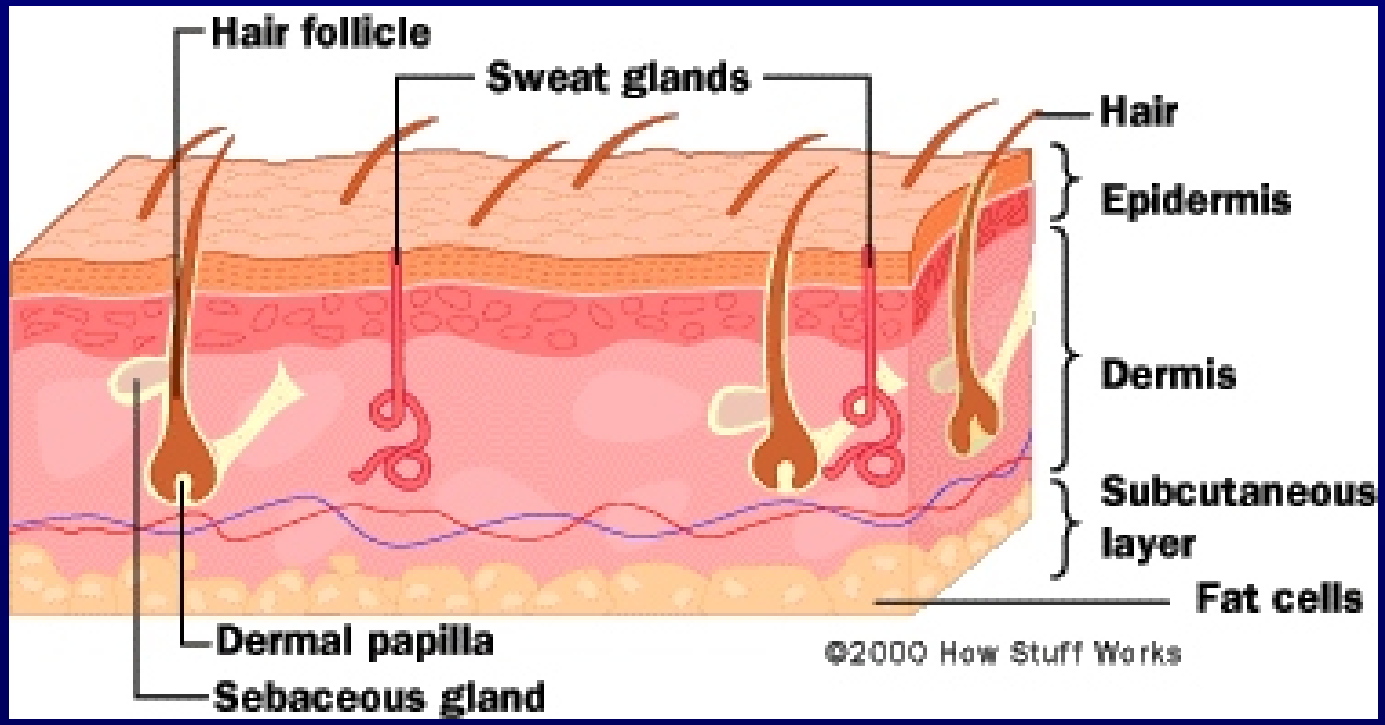
The student should be able to:

- List the two major factors to skin toxicology
- Name the most common cause of dermatitis
- Explain the difference between phototoxicity and photoallergy
- Explain the nature and treatment of fiber glass dermatitis

The two major factors of skin toxicology are:

- Its barrier effect
- Type IV - allergic contact dermatitis

SKIN


Hair follicle
Sweat glands
Hair
Epidermis
Dermis
Subcutaneous layer
Fat cells
Dermal papilla
Sebaceous gland
©2000 How Stuff Works

Contact dermatitis

either irritant or allergic

- represents 90% of all occupational dermatologic illness

Irritant Dermatitis

Not immunologic

- A direct affect by the agent
- Water - reduces protection of s.corneum and makes skin more susceptible to all insults.
- Cleansers, Alkalis, Acids, Oils, Organic solvents, Oxidant, Reducing agents, Plants

Allergic Contact dermatitis

- A type IV reaction
- Needs only small quantities to elicit reaction
- Original exposure, then re-exposure
- Low molecular weight compound
- Bound to a protein or transformed to become an allergen

Phototoxicity

- Not immunologically based but inflammation often occurs
- Photo activated to be an irritant
- Coal tar products
- Furocoumarins (psoralens)
- TCN, Sulfas, phenothaizines, thiazide

Photoallergy

- Similar to allergic contact dermatitis
- UVA -> substance "allergic" or "more allergic"
- Hexachloraphene, Benadryl, Musk
- Phenothiazines
- Sun screens (esp PABA), Ragweed, Chromium
- MANY PHOTOALLERGENS ARE PHOTOTOXIC IN HIGER DOSES

Fiber Glass Dermatitis

- Not allergic
- Happens with first exposure
- Goes away on its own
- Misdiagnosed as scabies
- Use scotch tape on skin; under microscope, can see fibers

Objectives for hematology

The student should be able to

- Understand the toxicology of red blood cells due to the oxidation of heme
- List what substances tend to oxidize heme
- Understand the toxicology of benzene, arsine, CO, and lead on the blood

RBC's have hemoglobin

Iron containing proteins -> 4 heme/polypeptide units

- Normal hemoglobin has Fe2+
- Methemoglobin (oxidized heme) has Fe3+
- Can't hold oxygen
- Results ↓ O_2 delivery or hemolysis of RBC
- Agents: Aniline, aromatic amines, nitrites, arsine, hydrazine

Benzene

Less use now that toxicity is known

- Petroleum products (e.g. gasoline, jet fuels)
- Prior to 1950 most common cause of toxic aplastic anemia
- AML CML ALL, multiple myeloma, myelodysplasia, but not CLL

Lead

- Anemia is a late sign of toxicity
  - Hypochromic, microcytic anemia, classically with basophilic stippling
- Porphyria like condition
  - Neurotoxicity, abdominal pain, constipation, vomiting
  - Heme precursors build up

Carbon Monoxide

- Odorless, colorless, nonirritating gas
- Incomplete combustion
- Mild often look like the "flu," w terrible headache
- Moderate to severe -> in coma and death
- Inhibiting oxygen delivery to tissues
- Ties up hemoglobin

Objectives for cardiovascular toxicology

The student should be able to understand and explain cardiovascular toxicology for

- CO, hydrogen sulfide, cyanide
- ethanol, cobalt, halogenated hydrocarbons
- organophosphate pesticides, carbon disulfide, thorium dioxide

Cardio tox

Halogenated Hydrocarbons

- Sensitize the myocardium to epinephrine
- ↑ risk of arrhythmias

Organophosphates

- Multiple effects -> Torsades de pointes
- Hypoxia 2^{0} to diaphragm paralysis

Cardio tox

- Hypoxia - Heart, brain, kidneys most energy/O_2 dependent
  - CO - limits O_2 availability
  - Cyanide, H_2S - poison cytochrome system
- Ethanol - direct toxin
  - Cobalt (in conjunction with EtOH)
- Nitrates
  - Potent vasodilators
  - Rebound constriction
  - Explosives in weapons may have nitrates (eg NTG)

Cadio tox

Carbon disulfide, Carbon Monoxide

- Accelerated athersclerotic disease
- CO
  - Methylene chloride
  - ?? Forklifts in warehouses (potential more than reality?)

Objectives for renal toxicology

The student should be able to explain, tell, or list:

- Why the kidney is at high risk for damage from toxins
- Correlation among different renal tests with site of injury
- What part of the kidney is at highest risk from renal toxins
- Common occupational toxicants to the renal / urinary system
- What is the most common cause of bladder cancer today.

Why the kidney is at high risk for damage from toxins

- High blood flow
- Toxins concentrated
- Bioactivation of hazards

Urinalysis

- Hematuria-> glomerular damage
- Glycosuria / Proteinuria-> tubular damage
- Volume / sp gravity extremes
  - Renal failure /tubule damage
- Medical surveillance
  - Creatinine and BUN very insensitive!
  - Consider retinol binding protein (sensitive and much easier to collect than beta2 microglobulin)

Sites of Renal Toxicity

- Proximal tubule most like to be damaged

Common, Occupationally-based Renal Hazards

- Heavy metals - Arsenic, Cadmium, Chromium, Lead, Mercury
- Halogenated solvents (some non-halogenated, too) especially halogenated degreasers

Objectives for liver toxicology

the student should be able to

- 1. Explain why the liver is at increased risk for toxic events from physiologic and metabolic standpoints
- 2. Understand that some liver toxin risks are idiosyncratic
- 3. Explain the usual progression of increasing liver damage
- 4. List the three major types of hepatic injury from viruses and know about their relative risk for cirrhosis
- 5. Explain how to choose tests to monitor exposure to liver toxins and how to interpret them

Liver

An organ at increased risk of toxic insult

- 30% of the cardiac output
- First organ to see many toxins
- Main organ for transformations
  - Can create more toxic substances

Liver Injury

- Usually dose related, with progressive architecture damage
  - Fatty->necrosis->fibrosis->cirrhosis->cancer
- Only occupational agent to cause cholestatic problems is METHYLENE DIANILINE (used in some composites)
- However, others are idiosyncratic
  - INH, halothane, and dilantin

Viral Liver Diseases

Most likely fatal occupational liver disease

- Hep A - no deaths, no cirrhosis, occupationally seen in 3rd world environments
- Hep B - highly communicable via blood and other body fluids
  - Significant risk of chronicity, cirrhosis and Ca
- Hep C - less contagious than B, significant carrier risk and risk of cirrhosis

Liver Lab Tests

- Usually use indirect measures
  - Enzymes usually measure cellular injury and death
  - Chem injury ALT (SGPT) is the best test
    – usually 2X AST for chemical hazards
  - Using lab normals for LFT's will be overly sensitive!!!!
  - EtOH ->AST (SGOT) is usually 2X SGPT
  - Alk Phos use for cholestatic toxins like MDA or when you don't want excessive sensitivity
  - Bilirubin and albumin are not of much value
  - GGT is too sensitive

Objectives of neurotoxicology

The student should be able to

- Identify the basic pathophysiology of acute and chronic neurotoxic effects
- Describe the general presentation of a chronic systematic neuropathy
- Recognize common compounds with neuropathic properties

Acute Encephalopathy

- Where – cerebral hemispheres
- What is seen? HA, irritable, disorientation, bizarre behavior
- What causes it? Acute exposure to many toxins at a high dose, especially solvents

Chronic Encephalopathy

- Where – cerebral hemispheres
- What is seen? HA, Cognitive difficulties, bizarre behavior
- What causes it? Chronic exposure to many toxins

Parkinsonian symptoms

- Basal ganglia and other extrapyramidal areas
- What is seen? Tremor, bradykinesias, rigidity
- What causes it? Manganese, CO, methanol

Motor neuron disease

- Spinal cord motor neurons
- What is seen? Weakness
- What causes it? Lead, manganese

Myeloneuropathies

- Spinal cord and peripheral nerves
- Paresthesias, sensory losses hyperreflexia, Babinski's sign (can look like MS!)
- Nitrous Oxide, organophosphates, n-hexane

Polyneuropathy

- Sensory and motor fibers, though usually sensory predominate
- Parethesias, numbness first, later weakness, loss of DTR's

Polyneuropathy

PREDOMINATELY SENOSRY LOSS

- Acrylamide - Sewer repairs
- Metals - Arsenic, thallium, mercury (golf course, grounds workers)
- Carbon Disulfide – Experimental chemists
- Ethylene Oxide - OR staff (equipment is malfunctioning or Cruise missle maintainers)
- PCB's - transformer workers, electricians

Polyneuropathy

MIXED NEUROPATHY (Sensory and Motor)

- Metals (with increased dose) Lead, arsenic, mercury - welders, plumbers, casters, workers who deal with manometers
- Hexacarbons (because the dose is so high) in aircraft repair
- Organophosphates

Polyneuropathy

PURE SENORY

- Cis Platin - patients, pharmacists, oncology nurses

Cranial neuropathy

- Thallium
- Trichlorethylene – Degreasers

- Time for a short break